WHAT IS CLAIMED IS:

1. A method for identifying an agent that modulates activity of the GRAIL complex in a cell, the method comprising:

combining a candidate biologically active agent with any one of:

(a) a complex comprising GRAIL and one or more of an otubain isoform; USP8 and ras-GRF1;

(b) a cell comprising a nucleic acid encoding and expressing an exogenous complex comprising GRAIL and one or more of an otubain isoform; USP8 and ras-GRF1; or

(c) a non-human animal model for GRAIL complex gene function comprising cells expressing one or more exogenous GRAIL complex gene sequence(s); and

determining the effect of said agent on anergy or cellular proliferation.

2. The method according to Claim 1, wherein said biologically active agent inhibits the ubiquitin ligase activity of GRAIL.

3. The method according to Claim 2, wherein said biologically active agent increases cellular proliferation.

4. The method according to Claim 1, wherein said biologically active agent increases the ubiquitin ligase activity of GRAIL.

5. The method according to Claim 4, wherein said biologically active agent decreases cellular proliferation.

6. The method according to Claim 1, wherein said biologically active agent binds to said complex comprising GRAIL and one or more of an otubain isoform; USP8 and ras-GRF1.

7. A method of determining the substrates of an E3 ligase, the method comprising:

introducing an E3 ligase coding sequence operably linked to an inducible promoter into a cell, wherein said cell is deficient in a negatively selectable enzyme;

introducing into a population of said cells a library of vectors comprising sequences encoding said negatively selectable marker fused to candidate E3 ligase substrate coding sequences;

induce expression of said E3 ligase in the presence of a compound toxic to cells expressing said enzyme;

wherein cells expressing said enzyme fused to a substrate for said E3 ligase are viable in the presence of said compound.

8. The method according to Claim 7, further comprising the step of rescuing said candidate E3 ligase substrate coding sequences.

9. The method according to Claim 7, wherein said rescue comprises specific PCR amplification.

10. The method according to Claim 7, wherein said negatively selectable enzyme is thymidine kinase.

11. The method according to Claim 7, wherein said E3 ligase is GRAIL.

12. An animal model for biological function of the GRAIL complex, comprising:

syngeneic bone marrow having a transgenic T cell receptor specificity, and comprising a vector encoding at least one protein selected from the group consisting of GRAIL, an otubain isoform; USP8 and ras-GRF1, operably linked to an inducible promoter.

13. A method of treating a proliferative disorder, said method comprising:

administering a therapeutic amount of a biologically active agent that modulates the activity of the GRAIL complex in an animal with a proliferative disorder.

14. The method according to Claim 13, wherein said proliferative disorder is a cancer.

15. The method according to Claim 13, wherein said proliferative disorder is an autoimmune disease.

16. The method according to Claim 15, wherein said autoimmune disease is systemic lupus erythematosus.

17. The method according to Claim 13, wherein said agent decreases the stability of GRAIL.

18. The method according to Claim 13, wherein said agent increases the ubiquitination of GRAIL.

19. The method according to Claim 13, wherein said agent increases the ubiquitination of ras-GRF1 by GRAIL.

20. An isolated polypeptide comprising an otubain isoform capable of stabilizing GRAIL.

21. An isolated polypeptide comprising an otubain isoform capable of destabilizing GRAIL.

22. An isolated polypeptide complex comprising GRAIL and one or more of an otubain isoform; USP8 and ras-GRF1.

23. A method of diagnosing a defect in immune tolerance, the method comprising determining the steady state level of GRAIL polypeptide, wherein a decrease in the level of GRAIL compared to a normally tolerant control cell is indicative of a defect in tolerance.

24. A method of diagnosing a defect in immune tolerance or cellular proliferation, the method comprising determining the level of an otubain isoform polypeptide, wherein an alteration in the level of said otubain isoform, compared to a normally tolerant control cell is indicative of said defect.